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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/878,131	06/08/2001	Guofan Hong	Lce113	1143

7590 10/20/2004
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EXAMINER

CHUNDURU, SURYAPRABHA

ART UNIT PAPER NUMBER

1637

DATE MAILED: 10/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/878,131	Applicant(s) HONG ET AL.	
	Examiner Suryaprabha Chunduru	Art Unit 1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 30 July 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-11 and 18-35 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-11 and 18-35 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. Applicants' response to the office action filed on July 30, 2004 has been entered.
2. Claims 1-11, 18-35 are pending.
3. This application is filed on June 8, 2001.

Response to Arguments

4. Applicant's response to the office action is fully considered and is found not persuasive.
5. The following is the rejection made in the previous office action under 35 USC 102(b):

Claims 9-11, 18-35 are rejected under 35 U.S.C. 102 (b) as being anticipated by Hong et al. (USPN. 5,834,253).

With reference to the instant claims 9-11, 22-23, 30-31, Hong et al. teach a method for extending an oligonucleotide primer annealed to a DNA template (double-stranded or single-stranded DNA) for direct cycle sequencing (classic Sanger one-step reaction) at temperatures between 45 C and 65 C and a melting temperature below about 80 C (see column 5, lines 1-17, column 12, lines 1-67, column 13, lines 1-7, column 18, lines 60-67, column 19, lines 1-49, column 20, lines 1-21) comprising (i) mixing a template with a primer (sequencing primer), four standard ddNTP terminators or their analogs, a DNA polymerase which has proof-reading 3'-5' exonuclease activity, such that the DNA polymerase functions to excise mismatched nucleotides from 3'-terminus of the DNA strand at a faster rate than the rate at which the DNA polymerase functions to remove nucleotides matched correctly with nucleotides of the template under conditions that DNA polymerase repeatedly extends the primer (see column 5, lines 2-12); (ii) effecting cycle primer extension reaction at temperature below 80 C (see column 5, lines 13, column 12, lines 8, 50-55, column 19, lines 3-5).

With regard to claims 9-11, 22-23, 30-31, Hong et al. also teach that the method comprises (i) DNA polymerase selected from *Bacillus stearothermophilus* (see column 5, lines 14-17, column 12, lines 14-24); Bst is functional within the temperature range between 25 C and 75 C (see column 12, lines 50-55, column 20, lines 4-12);

With regard to claims 22-23, 30-31, Hong et al. also teach use of fluorescent dye labeled nucleotides (see column 13, lines 1-7);

With regard to claims 22-23, 30-31, Hong et al. also teach that said DNA polymerase reduces the innate selective discrimination against the incorporation of nucleotide analogs such as ddNTPs, dITP and 7-deaza-dGTP (see column 12, lines 56-64);

With reference to the instant claims 18-21, 24-27, 32-35, Hong et al. teach that the method comprises DNA polymerase having homology (99-100%) to the instant claimed SEQ ID Nos. 1-4 (see sequence listing of patent '253 and attached sequence alignment);

With regard to claims 9-10, 22, 28, 30, Hong et al. disclose that the method comprises about 10% (w/v) glycerol, (see column 19, lines 6-11);

Thus the disclosure of Hong et al. meets the limitations in the instant claims.

Response to arguments:

Applicants' arguments with regard to the above rejection are fully considered and found not persuasive. Applicants' argue that the method as taught by Hong et al. does not teach repeated cycle extension of DNA and the single enzymatic DNA primer extension does not teach effective cycle primer extension reaction(s) at temperature below about 80 C. These arguments are fully considered and found not persuasive because first, the claims do not require repeated cycles because the claims recite cycle primer extension reaction for "a sufficient number of

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times”, which indicates single cycle could be a sufficient number for cycle primer extension and further the method as claimed and the method taught by Hong et al. use the same Bst DNA polymerase for cycle primer extension at temperature below about 80 C. Thus the method as taught by Hong et al. inherently teaches the property of the Bst DNA polymerase, that is, the repeatedly extending the primer and cycle primer extension. Applicants also argue that the Hong patent discloses the use of 50% glycerol as a preservative and does not teach its use as a melting agent. These arguments are fully considered and found not persuasive. Hong patent does disclose the use of about 10% (w/v) glycerol, (see column 19, lines 6-11) in the reaction mixture which inherently teaches its use as a melting agent. Finally Applicants’ argue that the DNA polymerase sequence similarities between the DNA polymerases of the Hong patent and the instant claimed Seq ID Nos. 1-4 does not teach cycle primer extension. These arguments are fully considered and found not persuasive because Examiner notes As MPEP 2112 states, “Products of identical chemical composition can not have mutually exclusive properties.” A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). In the instant context, since the DNA polymerase sequence is same as in the art, the properties are inherent and are inseparable. Thus that the method of Hong patent and the instant claims use the same Bst DNA polymerase with same sequence homology and hence the property of Bst polymerase in the Hong patent and the instant claims would be same. Thus the rejection is maintained herein as being anticipated by the disclosure of Hong patent.

6. Claims 1-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Walker (USPN. 5,712,124) in view of Hong et al. (USPN. 5,834,253).

With regard to claim 1-4, Walker teaches a method for extending an oligonucleotide primer or a pair of oligonucleotide primers using enzymatic cycle primer extension reaction (SDA) (see column 10, lines 4-67, column 11, lines 1-25) at temperatures between about 45⁰ C and about 65⁰ C and a melting temperature of about 70⁰ C (see column 10, lines 17-34), wherein the method comprises (i) the step of mixing a template with a primer or a pair of primers and a thermostable DNA polymerase (see column 10, lines 40-64), wherein, the DNA polymerase lacks 5'-3' exonuclease activity, is selected from the group consisting of *Bacillus stearothermophilus* (Bst) DNA polymerase (column 10, lines 3-16, lines 47-52) and extending the primer at cycle reaction temperature fluctuates between about 70⁰ C and about 37⁰ C (see column 10, lines 20-28). Walker also teaches that the reaction mixture can also contain glycerol, ethyl glycol (see column 10, lines 28-34).

With regard to claims 5-6, Walker also teaches that the method further comprises repeating the cycle primer extension, in the presence of a forward and a reverse primer to a template (see column 10, lines 58-64);

With regard to claim 7, Walker teaches that the forward and reverse primers have varying lengths (see column 12, lines 4-5).

However Walker did not specifically teach the proofreading 3'-5' exonuclease activity of Bst which functions to excise mismatched nucleotides from the 3' terminus of the DNA strand at

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a faster rate than the rate at which the DNA polymerase functions, and direct cycle sequencing using dideoxynucleotide terminators.

With reference to the instant claims 1-8, Hong et al. teach a method for replicating or amplification and sequencing DNA using a DNA polymerase having proofreading 3'-5' exonuclease activity and has the capability of removing mismatched nucleotides from the 3'-terminus of a newly formed DNA strand at a faster rate (see column 4, lines 42-67, column 5, lines 1-20) Hong et al. also teach that the method comprises sequencing cycle sequencing method (see column 12, lines 1-8, column 18, lines 60-67, column 19, lines 1-45) (i) about 10% (w/v) glycerol, (see column 19, lines 6-11); (ii) DNA polymerase selected from *Bacillus stearothermophilus* (see column 12, lines 14-24); method also comprises nucleotide analogs, such as ddNTPs, dITP (see column 12, lines 1-8).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the method of single cycle primer extension as taught by Walker with the proofreading 3'-5' exonuclease activity of Bst polymerase as taught by Hong et al. to achieve an expected benefit of developing a sensitive method for detecting the sequence of a target nucleic acid because Hong et al. taught the advantage of using Bst which has the proofreading 3'-5' exonuclease activity in addition to be suited work at low temperature (temperature range between 25⁰ C and 75⁰ C) reaction conditions (see column 19, lines 46-49, column 20, lines 1-12). An ordinary practitioner would have been motivated to combine the method of single cycle primer extension as taught by Walker with advantage of using Bst polymerase as taught by Hong et al. because inclusion of the proofreading property of Bst in the method of Walker would result in a sensitive method with high specificity to correct the

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misincorporation of mismatched nucleotides.

Response to arguments:

With regard to the above rejection Applicants' arguments are fully considered and found not persuasive. Applicants argue that Walker teaches a single temperature primer extension without cycling employing a DNA polymerase in conjunction with an endonuclease and teaches single temperature primer extension associated strand displacement amplification, and is irrelevant to the instant invention and would not be obvious to combine with Hong et al. to achieve the instant claimed repeated low temperature cycle extension. Applicants' arguments are fully considered and found not persuasive because the limitation upon which the arguments are based, that is *repeated* low temperature cycle extension is not in the instant claim 1 and the instant claim 1 does not require repeated cycling reaction. Further the Bst DNA polymerase as taught by Hong et al. can be used at low temperature primer extension. Thus it is prima facie obvious to one skilled in the art to modify single primer extension as taught by Walker with the addition of Bst DNA polymerase (with proof reading activity) for cycle primer extension to enhance the specificity of the primer extension method.

Conclusion

No claims are allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after

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the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Suryaprabha Chunduru whose telephone number is 571-272-0783. The examiner can normally be reached on 8.30A.M. - 4.30P.M, Mon - Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion reached on 571-272-0782. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and - for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

^{gpc}
Suryaprabha Chunduru
October 13, 2004


JEFFREY FREDMAN
PRIMARY EXAMINER

10/14/04